

Claim 1(original): A method of diagnosing or prognosticating a neurodegenerative disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:

- determining a level and/or an activity of
 - (i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
 - (ii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
 - (iii) a fragment, or derivative, or variant of said transcription or translation product,
- in a sample from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

Claim 2(original): A method of monitoring the progression of a neurodegenerative disease in a subject, comprising:

- determining a level and/or an activity of
 - (i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
 - (ii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
 - (iii) a fragment, or derivative, or variant of said transcription or translation product, in a sample from said subject and comparing said level and/or said activity to a reference value representing a known

disease or health status, thereby monitoring the progression of said neurodegenerative disease in said subject.

Claim 3(original): A method of evaluating a treatment for a neurodegenerative disease, comprising:

determining a level and/or an activity of

- (i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
- (ii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
- (iii) a fragment, or derivative, or variant of said transcription or translation product, in a sample from a subject being treated for said disease and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby evaluating said treatment for said neurodegenerative disease.

Claim 4(currently amended): The method according to claim 1 ~~any of claims 1 to 3~~ wherein said neurodegenerative disease is Alzheimer's disease.

Claim 5(currently amended): The method according to claim 1 ~~any of claims 1 to 4~~ wherein said sample is a cell, or a tissue, or a body fluid, in particular cerebrospinal fluid or blood.

Claim 6(currently amended): The method according to claim 1 ~~any of claims 1 to 5~~ wherein said reference value is that of a level and/or an activity of

- (i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
- (ii) a translation product of a gene coding for human

- MAGUIN-1 and/or human MAGUIN-2, and/or
- (iii) a fragment, or derivative, or variant of said transcription or translation product, in a sample from a subject not suffering from said neurodegenerative disease.

Claim 7 (currently amended): The method according to claim 1 ~~any of claims 1 to 6~~ wherein an alteration in the level and/or activity of a transcription product of the gene coding for human MAGUIN-1 and/or human MAGUIN-2 and/or a translation product of the gene coding for human MAGUIN-1 and/or human MAGUIN-2 and/or a fragment, or derivative, or variant thereof, in a sample cell, or tissue, or body fluid, in particular cerebrospinal fluid, from said subject relative to a reference value representing a known health status indicates a diagnosis, or prognosis, or increased risk of Alzheimer's disease in said subject.

Claim 8 (currently amended): The method according to claim 1 ~~any of claims 1 to 7~~, further comprising:

comparing a level and/or an activity of

- (i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
- (ii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
- (iii) a fragment, or derivative, or variant of said transcription or translation product, in a series of samples taken from said subject over a period of time.

Claim 9 (original): The method according to claim 8, wherein said subject receives a treatment prior to one or more of said sample gatherings.

Claim 10(original): The method according to claim 9 wherein said level and/or activity is determined before and after said treatment of said subject.

Claim 11(original): A kit for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining the propensity or predisposition of a subject to develop such a disease, said kit comprising:

- (a) at least one reagent which is selected from the group consisting of
 - (i) reagents that selectively detect a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and
 - (ii) reagents that selectively detect a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2 and
- (b) an instruction for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of a subject to develop such a disease by
 - (i) detecting a level, or an activity, or both said level and said activity, of said transcription product and/or said translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2 in a sample from said subject; and
 - (ii) diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of said subject to develop such a disease, wherein a varied level, or activity, or both said level and said activity, of said transcription

product and/or said translation product compared to a reference value representing a known health status; or a level, or activity, or both said level and said activity, of said transcription product and/or said translation product similar or equal to a reference value representing a known disease status indicates a diagnosis or prognosis of a neurodegenerative disease, in particular Alzheimer's disease, or an increased propensity or predisposition of developing such a disease.

Claim 12(original): A method of treating or preventing a neurodegenerative disease, in particular Alzheimer's disease, in a subject comprising administering to said subject in a therapeutically or prophylactically effective amount an agent or agents which directly or indirectly affect an activity and/or a level of (i) a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (ii) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iv) a fragment, or derivative, or variant of (i) to (iii).

Claim 13(original): A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of (i) a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (ii) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iv) a fragment, or derivative, or variant of (i) to (iii).

Claim 14(original): A pharmaceutical composition comprising a modulator according to claim 13.

Claim 15(original): Use of a modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of (i) a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (ii) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iv) a fragment, or derivative, or variant of (i) to (iii) for a preparation of a medicament for treating or preventing a neurodegenerative disease, in particular Alzheimer's disease.

Claim 16(original): A recombinant, non-human animal comprising a non-native gene sequence coding for human MAGUIN-1 and/or human MAGUIN-2 or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:

- (i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and
- (ii) introducing said targeting construct into a stem cell of a non-human animal, and
- (iii) introducing said non-human animal stem cell into a non-human embryo, and
- (iv) transplanting said embryo into a pseudopregnant non-human animal, and
- (v) allowing said embryo to develop to term, and
- (vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and
- (vii) breeding the genetically altered non-human animal of

step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.

Claim 17(original): Use of the recombinant, non-human animal according to claim 16 for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.

Claim 18(original): An assay for screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

- (i) a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
- (ii) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
- (iii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
- (iv) a fragment, or derivative, or variant of (i) to (iii), said method comprising:
 - (a) contacting a cell with a test compound;
 - (b) measuring the activity and/or level of one or more substances recited in (i) to (iv);
 - (c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and
 - (d) comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein

an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

Claim 19(original): A method of testing a compound, preferably of screening a plurality of compounds, for inhibition of binding between a ligand and human MAGUIN-1 and/or human MAGUIN-2, or fragments, or derivatives, or variants thereof, said method comprising the steps of:

- (i) adding a liquid suspension of said human MAGUIN-1 and/or human MAGUIN-2, or fragments, or derivatives, or variants thereof, to a plurality of containers;
- (ii) adding a compound, preferably a plurality of compounds, to be screened for said inhibition of binding to said plurality of containers;
- (iii) adding a detectable ligand, in particular a fluorescently detectable ligand, to said containers;
- (iv) incubating the liquid suspension of said human MAGUIN-1 and/or human MAGUIN-2, or said fragments, or derivatives, or variants thereof, and said compound, preferably said plurality of compounds, and said ligand;
- (v) measuring amounts of detectable ligand or fluorescence associated with said human MAGUIN-1 and/or human MAGUIN-2, or with said fragments, or derivatives, or variants thereof; and
- (vi) determining the degree of inhibition by one or more of said compounds of binding of said ligand to said human MAGUIN-1 and/or human MAGUIN-2, or said fragments, or derivatives, or variants thereof.

Claim 20(original): A method of testing a compound, preferably of screening a plurality of compounds, to determine the degree of binding of said compound or compounds to human MAGUIN-1 and/or human MAGUIN-2, or to fragments, or derivatives, or variants thereof, said method comprising the steps of:

- (i) adding a liquid suspension of said human MAGUIN-1 and/or human MAGUIN-2, or fragments, or derivatives, or variants thereof, to a plurality of containers;
- (ii) adding a detectable compound, preferably a plurality of detectable compounds, in particular fluorescently detectable compounds, to be screened for said binding to said plurality of containers;
- (iii) incubating the liquid suspension of said human MAGUIN-1 and/or human MAGUIN-2, or said fragments, or derivatives, or variants thereof, and said compound, preferably said plurality of compounds;
- (iv) measuring amounts of detectable compound or fluorescence associated with said human MAGUIN-1 and/or human MAGUIN-2, or with said fragments, or derivatives, or variants thereof; and
- (v) determining the degree of binding by one or more of said compounds to said human MAGUIN-1 and/or human MAGUIN-2, or said fragments, or derivatives, or variants thereof.

Claim 21(original): A method for producing a medicament comprising the steps of (i) identifying a modulator of neurodegenerative diseases, in particular Alzheimer's disease, by a method according to claim 18 and (ii) admixing the modulator with a pharmaceutical carrier.

Claim 22(original): A method for producing a medicament comprising the steps of (i) identifying a compound as an inhibitor of binding between a ligand and a human MAGUIN-1 and/or human MAGUIN-2 gene product by a method according to claim 19 and (ii) admixing the compound with a pharmaceutical carrier.

Claim 23(original): A method for producing a medicament comprising the steps of (i) identifying a compound as a binder to a human MAGUIN-1 and/or human MAGUIN-2 gene product by a method according to claim 20 and (ii) admixing the compound with a pharmaceutical carrier.

Claim 24(currently amended): A medicament obtainable by any of the methods according to claim 21 ~~to 23~~.

Claim 25(currently amended): A medicament obtained by any of the methods according to claim 21 ~~to 23~~.

Claim 26(original): A protein molecule shown in SEQ ID NO.1 or SEQ ID NO.2, or a fragment, or derivative, or variant thereof, for use as a diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.

Claim 27(original): A protein molecule shown in SEQ ID NO. 1 or SEQ ID NO.2, or a fragment, or derivative, or variant thereof, for use as a screening target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.

Claim 28(original): An antibody specifically immunoreactive with an immunogen, wherein said immunogen is a protein molecule shown in SEQ ID NO. 1, or a fragment, or derivative, or variant thereof.

Claim 29(original): An antibody specifically immunoreactive with an immunogen, wherein said immunogen is a protein molecule shown in SEQ ID NO. 2, or a fragment, or derivative, or variant thereof.

Claim 30(currently amended): Use of an antibody of claim 28 ~~or 29~~, for detecting the pathological state of a cell in a sample from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell.